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Coexposure to toluene and p-xylene in man: uptake and elimination

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ABSTRACT Eight male subjects were experimentally exposed to toluene, p-xylene, and a combination of toluene and p-xylene in order to study the influence of coexposure and exposure to different levels of each solvent on their uptake and elimination. The exposures were performed for four hours at exposure levels equivalent to or lower than the Swedish threshold limit value for toluene, 300 mg/m^3 (3·2 mmol/m^3). During and after the exposure, solvent concentrations were measured in blood and in expired air. In addition, the pulmonary ventilation rate was measured during the exposure. Decreases in the blood/end exhaled air concentration ratio were found for both toluene and p-xylene when given in combination compared with separate exposure. The total solvent uptake relative to the exposure level was decreased after exposure to the higher solvent concentrations, and the apparent clearance was also decreased after exposure to the higher concentrations of solvent. Finally, the blood solvent concentrations were lower at the end of the exposure compared with the maximal concentration during each exposure condition. In the kinetics of toluene and p-xylene the total amount of toluene or p-xylene, or both, seems to be of major importance. The change in blood/end exhaled air concentration ratio may indicate an effect of coexposure.

Occupational exposure to organic solvents more commonly necessitates simultaneous exposure to several different solvents than to one only. Several observations indicate that the kinetics of the uptake and elimination of separate organic solvents may change when more than one solvent is present at the same time.

In the rat the in vivo metabolism of high doses of trichloroethylene,[1] n-hexane,[2] benzene,[3 4] styrene,[3 5] and methylene chloride[6] is inhibited by coexposure to toluene. The metabolism of toluene in the rat is likewise inhibited by simultaneous exposure to trichloroethylene and benzene.[1 4] In man toluene and benzene do not influence the metabolism of each other during short term exposure using exposure levels at the Swedish threshold limit value.[4] Nevertheless, a decrease in the rate of metabolism of toluene and of m-xylene has been shown in man after ingesting ethanol.[7 8] Phenobarbital treatment of rats before the administration of high doses of toluene or m-xylene enhances the rate of metabolism of the solvents,[2 3 9 10] an effect that has not been possible to replicate in man or in rats exposed to low doses of m-xylene.[9]

With this information to hand there seemed to be a need to study the effects on the uptake and elimination of commonly used organic solvents by simultaneous exposure to more than one solvent at a total level of exposure not exceeding the threshold limit value. In the present investigation subjects were exposed to toluene and p-xylene, both of which frequently occur in the industrial environment either singly or in combination as, for example, while working with thinners used for paints or in the printing trade. Furthermore, some metabolic interaction or dose dependent kinetics, or both, would be expected, especially at higher doses, since the main metabolic pathway is the same for toluene and xylene—namely, microsomal hydroxylation by cytochrome P-450 and further oxidation through alcohol and aldehyde dehydrogenases to the corresponding acid.[10–13] This metabolic pathway, like all enzymatically mediated processes, is limited by capacity. The main purpose of the present investigation was to study how the uptake and elimination of toluene and p-xylene in man were influenced by coexposure and by exposure to different levels of each solvent.

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Subjects, material, and methods

Eight healthy men (age 26–37, weight 59–74 kg, height 170–183 cm) with no occupational exposure to organic solvents, were examined for four hours during and for two hours after exposure to toluene or p-xylene, or both, under different conditions. The levels of exposure were chosen such that the total amount of solvent in the high level toluene exposure, T(H), the high level p-xylene exposure, X(H), and the combined exposure, T(C) + X(C), was equivalent to the Swedish threshold limit value of toluene, expressed in mg/m³. The solvent concentrations in the inspired air during these exposures, together with those at the low level exposures to toluene, T(L), and to p-xylene, X(L), are shown in table 1.

The experiments were carried out at intervals of two weeks and the subjects were exposed in pairs under standardised conditions in an exposure chamber (volume 12 m³, air change 10 times/h, inlet air flow 115 m³/h, outlet air flow 135 m³/h). Solvent vapour was generated by passing compressed air through solvent filled wash bottles at constant temperature (34·5°C) and the desired concentrations were obtained by diluting with fresh air. The concentration of solvent in the exposure chamber was continuously monitored using a spectrophotometric method (Miran IA, infrared detector). In addition, intermittent monitoring was performed using gas chromatography (Antec 464 LP, flame ionisation detector, 5% Bentone + 5% SP 1000 on Supelcoport, temperature 100°C, nitrogen flow 25 ml/min). The same gas chromatographic equipment was used to analyse samples of end exhaled (alveolar) air and expired air for calculating the uptake of the solvent.

During four periods of eight minutes equally distributed throughout the exposure, expired air was collected into bags made of polyester laminated aluminium foil for the determination of solvent concentration and pulmonary ventilation per unit time. The air volume was measured with a balanced spirometer and the amount of solvent taken up during each sampling period was calculated as the difference between the total amount of solvent in the inspired and expired air. The experimental error was estimated to be ±3%.[14] The total uptake during the whole exposure period was calculated from the mean amounts taken up during each eight minute period. End exhaled air was sampled at the end of a normal exhalation and its solvent concentration was determined. To collect end exhaled air the subject was asked to take three normal breaths through a glass tube (volume 35 ml) and to close it tightly at both ends immediately after the third exhalation.

Table 1 *Solvent concentrations in inspired air under different exposure conditions**

Exposure condition	*Solvent concentration in inspired air (mmol/m³)*
High level toluene exposure, T(H)	3·24 ± 0·02†
Low level toluene exposure, T(L)	2·17 ± 0·06
High level p-xylene exposure, X(H)	2·85 ± 0·02†
Low level p-xylene exposure, X(L)	0·95 ± 0·04
Coexposure T(C)	2·19 ± 0·03
Coexposure X(C)	0·93 ± 0·02
Control = fresh air	—

*Sequence of the exposure conditions T(H), X(H), T(C) + X(C), and fresh air was based on a Latin square 4× 4 design whereas low level exposures T(L) and X(L) were carried out as a later series of exposures.
†Corresponds to 300 mg/m³, the Swedish threshold limit value for toluene.

The total error when sampling during exposure was estimated to be ±10% of the mean value for toluene and ±13% for p-xylene. The corresponding values after the end of exposure were ±14% and ±19% respectively.

The analysis of solvent concentrations in the blood was carried out using capillary samples from a finger. When the specimens were collected during the exposure the volunteers held out a hand through a closeable hole (diameter 9 cm) in the chamber wall. The blood (50–250 μl) was collected in gas-tight citrate treated head space bottles with Teflon lined membranes. A standardised volume of distilled water was added to haemolyse the blood.[15] Blood volumes were determined by weighing, and the samples were analysed using a gas chromatograph (Perkin Elmer F45, flame ionisation detector, 5% OV-17 on Chromosorb G, temperature 110°C, nitrogen flow 25 ml/min) and head space analysis after equilibration of the solvent at 37°C for at least 30 minutes. To calculate the blood solvent concentrations, individual blood/air partition coefficients for toluene and p-xylene were determined in venous blood collected immediately before the onset of each exposure. The determination of individual partition coefficients was made from a 100 μl blood volume and solvent concentrations determined in other volumes were standardised to this volume. The error was estimated to be ±10% for the determination of toluene in blood and ±12% for p-xylene, the lower limit of detection was estimated to be 0·2 μmol/l for both toluene and p-xylene.

Student's two tailed *t* test for dependent observations was used to determine the significance of differences between mean values. The results are, unless otherwise stated, presented as mean values ± standard deviation. The calculation of the experimental error for a single determination was based on the differences between double determinations and expressed as a percentage of the mean value. Phar-

Table 2 *Pulmonary ventilation, V_E, total uptake, U_p, and relative uptake, F, under different exposure conditions**

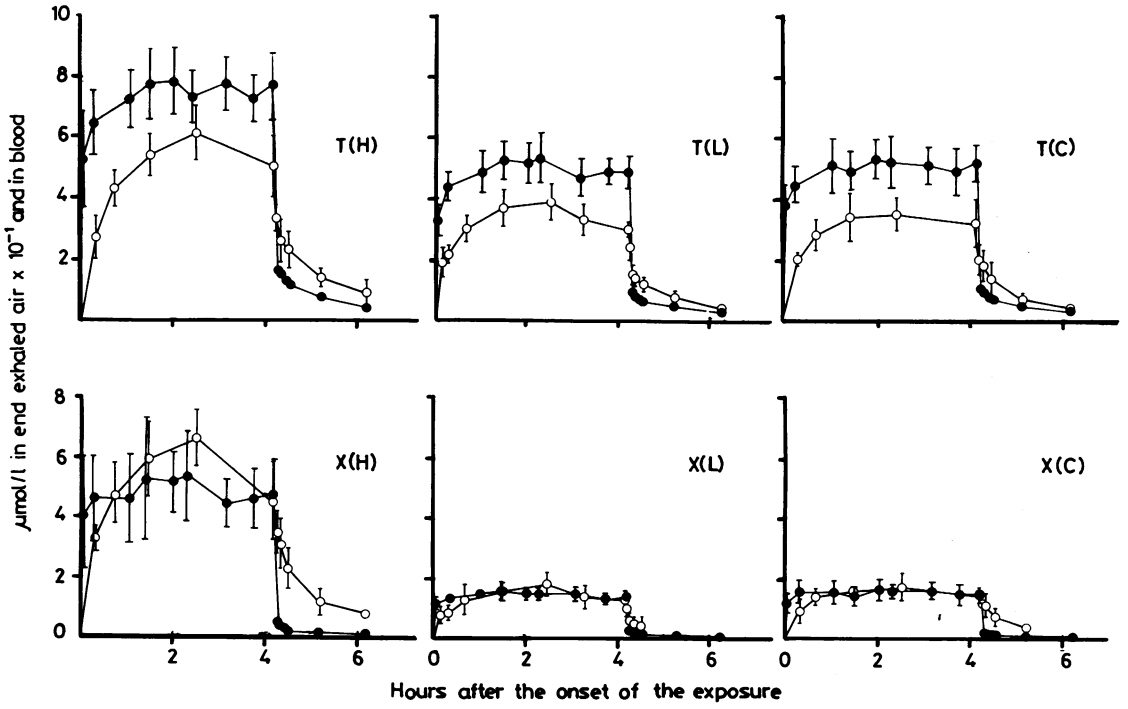
Exposure condition	*Pulmonary ventilation V_E (l/min)*	*Total uptake,† U_t = $V_E\, t(C_{in} - C_{ex})$ (mmol)*	*Relative uptake, $F = (C_{in} - C_{ex})\ 100/C_{in}$ (%)*
T(H)	6·9 ± 1·6	2·9 ± 0·9	54 ± 4
T(L)	8·8 ± 1·6	2·4 ± 0·4	54 ± 5
T(C)	6·7 ± 1·8	1·8 ± 0·5	52 ± 6
X(H)	7·2 ± 1·7	2·7 ± 0·5	58 ± 6
X(L)	9·0 ± 1·2	1·2 ± 0·1	60 ± 5
X(C)	6·7 ± 1·8	0·8 ± 0·2	55 ± 6
Control	7·1 ± 1·9	—	—

*Statistically significant differences between different exposure conditions: Pulmonary ventilation: T(H) ≤ T(L) $p = 0.05$, T(C) < T(L) $p < 0.05$, X(H) < X(L) $p < 0.01$, X(C) < X(L) $p < 0.01$. Relative uptake: X(C) < X(L) $p < 0.01$.
†t = duration of exposure, C_{in} = solvent concentration in inspired air, and C_{ex} = solvent concentration in expired air.

macokinetic calculations were based on those of Rowland and Tozer.[16]

Results

The mean relative uptake was 53% for toluene and 58% for p-xylene (table 2), and no differences were seen between the four periods of sampling during the same exposure. No statistically significant differences were noted in the relative uptake of toluene during the three types of exposure to toluene, but a decrease in the relative uptake of X(C) compared with X(L) was noted ($p < 0.01$). The total uptake, relative to the level of exposure, was smaller during both the T(H) and the T(C) conditions compared with that of T(L) and also during the X(H) and X(C) conditions compared with X(L) [T(H) < T(L) $p < 0.05$, T(C) < T(L) $p < 0.01$, X(H) < X(L) $p < 0.001$, X(C) < X(L) $p < 0.01$]. These variations are positively related to the variations in pulmonary ventilation at the different types of exposure. The pulmonary ventilation rate under the different



Mean values of solvent concentrations in end exhaled air (●) and in blood (○) during and after exposure to toluene or p-xylene or both. Exposure time: 250 minutes. Exposure levels: T(H) = 3·2 mmol/m³, T(L) = 2·2 mmol/m³, T(C) = 2·2 mmol/m³, X(H) = 2·8 mmol/m³, X(L) = 0·9 mmol/m³, and X(C) = 0·9 mmol/m³.

Table 3 *Values of apparent clearance, Cl_{app}, apparent systemic extraction ratio, E_{app}, and blood/air concentration ratios in vivo, N_{eff} and N**

Exposure condition	*Apparent clearance Cl_{app} = dose/AUC† (l/h·kg)*	*Apparent systemic extraction ratio‡ $E_{app} = Cl_{app}/Q_t$*	*Blood/air concentration ratios in vivo‡*		
			$N_{eff} = C_{blood}/C_{in}$	$N = C_{blood}/C_A$	$N = N_{eff}/(1-N_{eff}E_{app}\cdot Q_t/\dot{V}_A)$
T(H)	1·7 ± 0·4	0·38	1·9 ± 0·3	8·2 ± 1·2	7·2
T(L)	2·3 ± 0·4	0·52	1·8 ± 0·3	7·5 ± 1·4	7·0
T(C)	1·8 ± 0·5	0·40	1·6 ± 0·3	6·9 ± 0·8	5·2
X(H)	1·6 ± 0·4	0·36	2·3 ± 0·3	15·1 ± 3·0	14·8
X(L)	2·6 ± 0·6	0·60	1·9 ± 0·4	12·6 ± 2·1	17·4
X(C)	1·6 ± 0·4	0·36	1·6 ± 0·3	10·0 ± 2·4	5·7

*Statistically significant differences between different exposure conditions. Apparent clearance: T(H) < T(L) $p < 0·01$, T(C) < T(L) $p < 0·05$, X(H) < X(L) $p < 0·01$, X(C) < X(L) $p < 0·01$. Blood/end exhaled air concentration ratio (C_{blood}/C_A): T(H) > T(C) $p < 0·05$, X(H) > X(C) $p < 0·001$, X(C) < X(L) $p < 0·05$.
†AUC = Area under the blood concentrations against time curve was calculated by the trapezoidal rule during the exposure and during the elimination phase by integration of the equation $y = Ae^{\alpha t} + Be^{\beta t}$ where y is the solvent concentration in the blood, t represents the time, A and B are the y-intercepts, and α and β slopes of lines. The terminal phase was disregarded.
‡Q_t = 4·4 l/h kg (based on the body weight 68·5 kg).

exposure conditions did not differ from that during the non-solvent exposure with the exception of X(L) when the rate was higher ($p < 0·05$).

The blood solvent concentration reached its maximum at about 150 minutes after the onset of the exposure (fig) and decreased during the later part of the exposure irrespective of the exposure conditions (decrease from 150 min to 250 min after onset of exposure: T(H) $p < 0·01$, T(L) $p < 0·001$, T(C) $p < 0·05$, X(H) $p < 0·001$, X(L) $p < 0·01$, X(C) $p < 0·05$; one tailed test). Table 3 gives the concentration ratios between the solvent concentration in the blood and that in the end exhaled air at the time of maximal blood solvent concentration (N). The concentration ratio calculated from exposure condition T(H) was higher than that from T(C), that from X(H) was higher than from X(C), and that from X(C) was lower than from X(L). No difference could be found from exposure conditions T(H) and T(L), T(C) and T(L), or X(H) and X(L). The concentration ratios can also be expressed as the ratio between the solvent concentration in the blood and in the inspired air, N_{eff}. Compared with N, significantly lower values were then obtained (table 3) but the pattern of variation was similar for both N_{eff} and N.

An apparent clearance per kg body weight (Cl_{app}) was calculated as the total amount of solvent taken up divided by the area under the blood concentration against time curve (table 3) Cl_{app} showed the same pattern of variation during the toluene and p-xylene exposures with the highest values being found during the low dose exposures.

The apparent systemic extraction ratio (E_{app}) was calculated from the Cl_{app} and the cardiac output, Q_t, as Cl_{app}/Q_t where Q_t equals 5 l/min[17] (table 3). Concentration ratios between blood solvent concentration and end exhaled air may be expressed as $N = N_{eff}/(1-N_{eff}\ E_t\ Q_t/\dot{V}_A)$,[18] where $\dot{V}_A$, the alveolar pulmonary ventilation, equals $\dot{V}_E \cdot 2/3$. These ratios (assuming E_{app} equals the systemic extraction ratio, E_t) are given in table 3 for comparison with those derived from in vivo experiments.

Discussion

The uptake of solvent by man during whole body exposure to toluene and xylene occurs almost exclusively through the lungs; dermal uptake represents about 1% of the total uptake.[19] During a defined exposure time, t, and exposure level, C_{in}, the uptake, U_t, is determined by (*a*) the alveolar pulmonary ventilation rat, $\dot{V}_A$, (*b*) the blood/air partition coefficient of the solvent, N, and (*c*) the ratio between the solvent concentration in the arterial blood and in the inspired air, N_{eff}. The uptake can thus be calculated as $U_t = \dot{V}_A\ (N-N_{eff})C_{in}\ t/N$ when $N = N_{eff}/(1-N_{eff}\ E_t\ Q_t/\dot{V}_A)$.[18] The estimated value of N agrees reasonably well with the blood/air concentration ratio obtained in vivo in this study. The values of N do not reach the blood/air partition coefficients obtained in vitro (16 and 38 for toluene and p-xylene, respectively[20]); indicating that this coefficient and N are not completely equivalent. One explanation for this discrepancy could be incomplete equilibration of the solvent in arterial blood and in alveolar air. The values of the in vitro coefficient have been shown in our laboratory to be reached more readily during physical exercise than during rest.[17,21] The concentration ratio in vivo at rest has been determined as 9 for toluene with an exposure level of 300 mg/m³ (3·2 mmol/m³),[21] and 15 for xylene at 435 mg/m³ (4·1 mmol/m³).[22] The concentration ratios in vivo during simultaneous exposure to toluene and p-xylene in the present study were decreased compared with exposure to

each solvent at high level. In vitro no change in the blood/air partition coefficient of toluene could be seen during coincubation with benzene.[4]

No statistically significant differences were seen in the relative uptake (F) during coexposure when compared with the high level exposure to each solvent despite the difference noted in the blood/air concentration ratios. A decrease in F was seen for p-xylene, however, during coexposure when compared with the low level exposure. A similar trend was seen during the corresponding toluene exposures. The decrease in F is probably best explained by a corresponding decrease in the value of $\dot{V}_A/\dot{V}_E$ in the equation: $F = \dot{V}_A(N\text{-}N_{eff})/\dot{V}_E N$ [$T(C) < T(L)$ $p < 0{\cdot}05$, $X(C) < X(L)$ $p < 0{\cdot}01$]. The ratio $(N\text{-}N_{eff})/N$ remained constant for the different toluene and p-xylene exposure conditions.

An influence on $\dot{V}_A/\dot{V}_E$ may also explain the discrepancies between the experimental and estimated values of N, where, for the latter, values of $\dot{V}_A/\dot{V}_E$ was considered to be constant (table 3). Toluene and p-xylene at exposure levels below or equivalent to the Swedish threshold limit value are not reported to affect lung function at rest.[23] Available data merely describe a dose dependent effect on the respiratory rate in mice with large doses of toluene and xylene[24 25] and an acute narcotic effect in man due to high level exposure to organic solvents.[26]

When calculating the apparent clearance, the total uptake of solvent was taken as the dose since small non-ionised lipophilic molecules have the ideal properties to facilitate rapid diffusion across the alveolar membrane into the blood[27]; the liver is considered to be the predominant metabolising organ because of its high level of enzymatic activity. The fact that toluene and p-xylene are both excreted mainly as metabolites[12 13] and are good substrates for hepatic microsomal cytochrome P-450,[28 29] indicates that the total blood flow through the liver, 1·6 l/min,[17] might be the limiting factor in their in vivo kinetics; perfusion limited kinetics have been suggested for several organic solvents.[18] In addition to almost complete hepatic extraction, the values of Cl_{app} ($\geq$1·8 l/min) presumably represent an extrahepatic metabolism, a pulmonary excretion of unmetabolised solvent (4–18% of toluene, 4–5% of p-xylene[12 21 22]), and an uptake in adipose tissue[21 30] or other tissues. The value of Cl_{app}, 2·3 l/h·kg, found during low level exposure to toluene is the same as that obtained previously for toluene after a comparable dose of solvent [toluene 100 ppm (4·0 mmol/m³) and benzene 25 ppm (1·0 mmol/m³) for two hours].[31] The lowest level of solvent exposure, X(L), resulted in a higher value of Cl_{app}, 2·6 l/kg·h, whereas the high level exposures resulted in the lowest values.

E_t can be estimated in two ways in addition to that mentioned previously (Cl_t/Q_t when Cl_t is the total clearance)—namely, from the equations $E_t = \dot{V}_A(N\text{-}N_{eff})/Q_t N N_{eff}$ and $E_t = (C_a - C_v)/C_a$ where C_a is the solvent concentration in the arterial blood and C_v that in mixed venous blood determined from the equation $C_v = C_a - \dot{U}_t/Q_t$.[18] Regardless of the equation used, E_t or E_{app} equals 0·4 in the high level exposures and 0·5 or more in the low level exposures. Consequently, both toluene and p-xylene may have dose dependent kinetics.

The theory that toluene and p-xylene have the same route of elimination is supported by the extraction ratios obtained. The metabolic turnover for toluene and xylene in vitro is similar to that of styrene.[29] An increase in the uptake of styrene in the blood against time that is not linearly correlated to the increase in exposure level over the range of 200 to 600 ppm (8·1–24·2 mmol/m³) has been demonstrated in rats.[32] After exposure to m-xylene, 800 mg/m³ (7·5 mmol/m³), dose dependent kinetics based on the enzymatic induction by phenobarbital have been found in rats.[9] Furthermore, there is evidence that, in man, the metabolic rate of tetrachloroethylene is limited by capacity at exposure levels exceeding 100 ppm (4·2 mmol/m³)[33] and that the metabolism of methylene chloride in rats is saturated at exposures in the range 50–1500 ppm (2·1–630·2 mmol/m³).[34] Nevertheless, phenobarbital treatment does not cause induction in human subjects exposed to m-xylene, 400 mg/m³ (3·8 mmol/m³).[9] In the present study it was possible to detect dose dependent changes in Cl_{app} at exposure levels between 0·9–3·2 mmol/m³. In addition to saturated metabolism this may be due, for example, to changes in tissue perfusion.

The decrease in the blood solvent concentration during the latter part of the exposure may, apart from changes in tissue perfusion, be explained by stimulation of metabolising enzymes. Both toluene[35] and xylene[11 28 36 37] are known to exert an influence on their metabolising enzymes in rodents. There are also data showing enzyme induction in connection with occupational exposure to styrene and acetone (maximum air concentrations 164 mg/m³ (1·6 mmol/m³) and 571 mg/m³ (9·8 mmol/m³), respectively).[38]

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References

[1] Ikeda M. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. *Int Arch Occup Environ Health* 1974;**33**:125–30.

[2] Perbellini L, Leone R, Fracasso ME, Burgnone F, Venturini MS. Metabolic interaction between n-hexane and toluene in vivo and in vitro. *Int Arch Occup Environ Health* 1982;**50**:351–8.

[3] Ikeda M, Ohtsuji H, Imamura T. In vivo suppression of benzene and styrene oxidation by co-administered toluene in rats and effects of phenobarbital. *Xenobiotica* 1972;**2**:101–6.

[4] Sato A, Nakajima T. Dose-dependent metabolic interaction between benzene and toluene in vivo and in vitro. *Toxicol Appl Pharmacol* 1979;**48**:249–56.

[5] Ikeda M, Hirayama T. Possible metabolic interaction of styrene with organic solvents. *Scand J Work Environ Health* 1978;**4**, suppl 2:41–6.

[6] Ciuchta HP, Savell GM, Spiker RC Jr. The effect of alcohols and toluene upon methylene chloride-induced carboxyhemoglobin in the rat and monkey. *Toxicol Appl Pharmacol* 1979; **49**:347–54.

[7] Waldron HA, Cherry N, Johnston JD. The effects of ethanol on blood toluene concentrations. *Int Arch Occup Environ Health* 1983;**51**:365–9.

[8] Riihimäki V, Savolainen K, Pfäffli P, Pekari K, Sippel HW, Laine A. Metabolic interaction between m-xylene and ethanol. *Arch Toxicol* 1982;**49**:253–63.

[9] David A, Flek J, Frantik E, Gut I, Sedivec V. Influence of phenobarbital on xylene metabolism in man and rats. *Int Arch Occup Environ Health* 1979;**44**:117–25.

[10] Ikeda M, Ohtsuji H. Phenobarbital-induced protection against toxicity of toluene and benzene in the rat. *Toxicol Appl Pharmacol* 1971;**20**:30–43.

[11] Patel JM, Harper C, Drew RT. The biotransformation of p-xylene to a toxic aldehyde. *Drug Metab Dispos* 1978;**6**:368–74.

[12] Sedivec V, Flek J. The absorption, metabolism, and excretion of xylenes in man. *Int Arch Occup Environ Health* 1976;**37**:205–17.

[13] Williams RT. *Detoxication mechanisms*. New York: Wiley, 1959: 194–6.

[14] Wigaeus E, Löf A, Bjurström R, Byfält Nordqvist M. Exposure to styrene. Uptake, distribution, metabolism and elimination in man. *Scand J Work Environ Health* 1983;**9**:479–88.

[15] Radzikowska-Kintzi H, Jakubowski M. Internal standardization in the head space analysis of organic solvents in blood. *Int Arch Occup Environ Health* 1981;**49**:115–23.

[16] Rowland M, Tozer TN. *Clinical pharmacokinetics. Concepts and applications*. Philadelphia: Lea and Febiger, 1980.

[17] Åstrand I. Effect of physical exercise on uptake, distribution and elimination of vapors in man. In: V Fiserova-Bergerova, ed. *Modeling of inhalation exposure to vapors: uptake, distribution, and elimination*. Vol 2. Boca Raton: CRC Press Inc, 1983:107–30.

[18] Andersen M. A physiologically based toxicokinetic description of the metabolism of inhaled gases and vapors: analysis at steady state. *Toxicol Appl Pharmacol* 1981;**60**:509–26.

[19] Riihimäki V, Pfäffli P. Percutaneous absorption of solvent vapors in man. *Scand J Work Environ Health* 1978;**4**:73–85.

[20] Sato A, Nakajima T. Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. *Br J Ind Med* 1979;**36**:231–4.

[21] Carlsson A. Uptake, distribution and elimination of methylene chloride and toluene. *Arbete och Hälsa* 1982;**3**:1–41.

[22] Åstrand I, Engström J, Övrum P. Exposure to xylene and ethylbenzene. *Scand J Work Environ Health* 1978;**4**:185–94.

[23] von Oettingen W, Neal P, Donahue D. The toxicity and potential dangers of toluene. *JAMA* 1942;**118**:579–84.

[24] Damgård Nielsen G, Alarie Y. Sensory irritation, pulmonary irritation, and respiratory stimulation by airborne benzene and alkylbenzenes: prediction of safe industrial exposure levels and correlation with their thermodynamic properties. *Toxicol Appl Pharmacol* 1982;**65**:459–77.

[25] Carpenter CP, Kinkead ER, Geary DL Jr, Sullivan LJ, King JM. Petroleum hydrocarbon toxicity studies. V. Animal and human response to vapors of mixed xylenes. *Toxicol Appl Pharmacol* 1975;**33**:543–58.

[26] Browning E. *Toxicity and metabolism of industrial solvents*. New York: Elsevier, 1965.

[27] Åstrand I. Uptake of solvents in the blood and tissues of man: a review. *Scand J Work Environ Health* 1975;**1**:199–218.

[28] Carlone M, Fouts JR. In vitro metabolism of p-xylene by rabbit lung and liver. *Xenobiotica* 1974;**4**:705–15.

[29] Sato A, Nakajima T. A vial-equilibration method to evaluate the drug-metabolizing enzyme activity for volatile hydrocarbons. *Toxicol Appl Pharmacol* 1979;**47**:41–6.

[30] Engström J, Bjurström R. Exposure to xylene and ethylbenzene. *Scand J Work Environ Health* 1978;**4**:195–203.

[31] Sato A, Nakajima T, Fujiwara Y, Hirosawa K. Pharmacokinetics of benzene and toluene. *Int Arch Occup Environ Health* 1974;**33**:169–82.

[32] Ramsey J, Young J. Pharmacokinetics of inhaled styrene in rats and humans. *Scand J Work Environ Health* 1978;**4**, suppl 2:84–91.

[33] Ohtsuki T, Kunihiko S, Koizumi A, Kumai M, Ikeda M. Limited capacity of humans to metabolize tetrachloroethylene. *Int Arch Occup Environ Health* 1983;**51**:381–90.

[34] McKenna MJ, Zempel JA, Braun WH. The pharmacokinetics of inhaled methylene chloride in rats. *Toxicol Appl Pharmacol* 1982;**65**:1–10.

[35] Pyykkö K. Time-course of effects of toluene on microsomal enzymes in rat liver, kidney and lung during and after inhalation exposure. *Chem Biol Interact* 1983;**44**:299–311.

[36] Smith BR, Bend JR. Metabolic interactions of hydrocarbons with mammalian lung. *Reviews of Biochemistry and Toxicology* 1981;**3**:77–122.

[37] Toftgård R, Nilsen OG. Effects of xylene and xylene isomers on cytochrome P-450 and in vitro enzymatic activities in the rat liver, kidney and lung. *Toxicology* 1982;**23**:197–212.

[38] Dolara P, Lodovici M, Salvadori G, Santoni G, Caderni G. Enzyme induction in humans exposed to styrene. *Ann Occup Hyg* 1983;**27**:183–8.